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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/675,470	09/30/2003	Joseph W. Harding		5566

7590 06/17/2004

John C. Hughs
Patent Attorney
440 N. Volland St., B205
Kennewick, WA 99336

EXAMINER	
NICKOL, GARY B	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 06/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/675,470	HARDING ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *1-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Re: Harding *et al.*

Date of priority: 09/30/2003

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-7, drawn to a method of *increasing* angiogenesis in pathological conditions associated with insufficiencies in vascular perfusion comprising the administration of an AT_4 receptor agonist, classified in class 514, subclass 1;class 424, subclass 184.1.

II. Claims 8-28, drawn to a method of *inhibiting* angiogenesis and or the growth and metastasis of solid tumors comprising the administration of an AT_4 receptor antagonist, classified in class 514, subclass 1; class 424, subclass 184.1.

The inventions are distinct, each from the other because of the following reasons:

The inventions of Groups I-II are drawn to materially distinct methods which differ at least in objectives, method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success. For example, Group I is drawn to a method of increasing angiogenesis which involves different objectives, different reagents (an agonist), and different criteria for success

versus a method of inhibiting angiogenesis. The latter further comprises different materially distinct steps in that tumor growth and metastasis are assayed.

Because these inventions are distinct for the reasons given above and the search required for one group is not required for another group, restriction for examination purposes as indicated is proper.

During a telephone conversation with John Hughs on May 21, 2004 a provisional election was made without traverse to prosecute the invention of Group II, claims 8-28. **Affirmation of this election must be made by applicant in replying to this Office action**. Claims 1-7 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 8-28 are currently pending and are under consideration.

Specification

The specification is objected to on page 16, (2nd to last line) for what appears to be an improper disclosure of an amino acid sequence without a respective sequence identifier, i.e. a SEQ ID NOs:. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821 through 1.825. In the absence of a sequence identifier for each sequence, Applicant must provide a computer readable form (CRF) copy of the sequence listing, an initial or substitute paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a

statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e-f) or 1.825(b) or 1.825(d). Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. (see MPEP 2422).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth methods of inhibiting angiogenesis and or growth and metastasis of cancers, including breast cancer comprising administering an AT_4 receptor antagonist wherein said antagonist is the compound Nle^1,Leu^3-Ψ-$(CH_2$-$NH_2)^{3-4}$-AngIV (NORLEUAL). Thus, the written description is not commensurate in scope with the claims drawn to a **genus** of antagonists that antagonize the AT_4 receptor which inhibit angiogenesis and inhibit the growth and metastasis of cancers.

The specification fails to define the limitations of molecules which can be considered as antagonists of the invention. The specification only teaches (page 7) that the present invention relates to the general utility of AT_4 receptor ligands to alter angiogenesis and in particular those ligands that inhibit angiogenesis. The specification defines (page 16) an AT_4 receptor ligand as any molecule that can compete for the binding of the radiated natural ligand, ^{125}I-angiotensin IV. (CHECK FOR SEQ COMPLIANCE- on page 16). However, the written description only reasonably conveys one species of an antagonist ($\underline{Nle^1,Leu^3\text{-}\Psi\text{-}(CH_2\text{-}NH_2)^{3\text{-}4}\text{-}AngIV}$) of an AT_4 receptor antagonist with the biological properties as claimed. The instant disclosure of a single species of AT_4 antagonist fails to adequately describe the scope of the claimed genus (any and all AT4 antagonists), which encompasses a substantial variety of subgenera-, i.e. any molecule that that can compete for the binding of the natural ligand ---such as peptides, organic molecules, and antibodies. A description of a genus of antagonists may be achieved by means of a recitation of a representative number of antagonists, *defined* by structure, falling within the scope of the genus. However, the instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of antagonists that would distinguish the claimed antagonists from other molecules that do not have the claimed biological properties. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of one species of antagonist is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of antagonists, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only methods of inhibiting angiogenesis and or growth and metastasis of cancers, including breast cancer comprising administering an AT_4 receptor antagonist wherein said antagonist is the compound Nle^1,Leu^3-Ψ-$(CH_2$-$NH_2)^{3-4}$-AngIV, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, **or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.**

Claims 8-11, 13-18, 20-21 are rejected under 35 U.S.C. 102(e) as being anticipated by WO 03/011304 A1 (Albiston *et al.*, October 17, 2001).

Albiston *et al.* teach methods of treating or preventing disease conditions associated with altered activity of the AT4 receptor comprising administering an effective amount of a compound that modulates the activity of the AT4 receptor (page 7, line 15). By modulating, the prior art teaches (page 9, line 1+) those compounds that are able to decrease or increase the biological activity of the receptor. Hence, the methods encompass antagonistic or "interfering"- see page 85, line 31- compounds. By diseased conditions, the prior art anticipates the treatment of "cancer" and "inhibition of angiogenesis" (page 8, lines 3 and 7; page 85, lines 20-35; page 100; page). The reference further teaches a variety of routes of administration including intravenous, subcutaneous, intramuscular, intrathecal, intraventricular, oral, and topical administration (page 13, line 9+). It is assumed for examination purposes that a topical administration would meet the limitations of a "local" administration since the specification does not specifically define the limitations of a "local" administration. It is further assumed for examination purposes that the prior art teaching of intravenous and intraventricular injections

anticipates and or is encompassed by an intravascular administration since the specification does not specifically define the limitations of intravascular administrations.

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 8, 11, 15, 18, 22 and 25 are rejected under 35 U.S.C. 102(a) as being anticipated by Masino, J.A. ("Identification of the Angiotensin IV Receptor Antagonist, Norleual, as a Novel Inhibitor of Angiogenesis and Tumor Growth", Dissertation Abstracts International, May 2003, Vol. 64, No. 7B).

Masino teaches a method of inhibiting angiogenesis in pathological conditions where increased angiogenesis and coincidental vascular perfusion are clinically detrimental; including inhibiting the growth and metastasis of solid tumors; further including inhibiting the growth and metastasis of breast cancer comprising producing an AT4 receptor antagonist (NORLEUAL, page 30; page 39) and administering the AT4 receptor antagonist wherein the delivery of the AT4 receptor antagonist is intramuscularly (page 39, line 9).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masino, J.A. ("Identification of the Angiotensin IV Receptor Antagonist, Norleual, as a Novel Inhibitor of Angiogenesis and Tumor Growth", Dissertation Abstracts International, May 2003, Vol. 64, No. 7B) **or,** in the alternative, over WO 03/011304 A1 (Albiston *et al.*, October 17, 2001) in view of US Patent No. 5,219,883 (Koszyk *et al.*, June 15, 2003, column 5).

1. Masino J.A. teaches as set forth above with regards to claims 8, 11, 15, 18, 22 and 25.
2. Albiston *et al.* teach as set forth above with regards to claims 8-11, 13-18, 20-21
3. Neither Masino J.A. or Albiston *et al.* specifically include certain routes of administration. For example, Masino doesn't teach local, intravascular, intraperitoneal, subcutaneous, or oral. And, Albiston *et al.* doesn't teach intraperitoneal.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modulate the method of Masino or Albiston *et al.* so as to include other well-known and conventional routes of clinical administration. One would have been motivated to do so because such routes of administration are conventional in the art as so evidenced by Koszyk *et al.* (US Patent No. 5219883, column 5) and would have provided one with a reasonable expectation of success.

No claim is allowed.

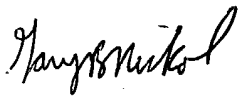
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 571-272-0835. The examiner can normally be reached on M-Th, 8:30-5:30; alternate Fri., 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary B. Nickol Ph.D.
Primary Examiner
Art Unit 1642

June 10, 2004



GARY NICKOL
PRIMARY EXAMINER